REMARKS

1. Amendments to Claims

Claims 57, and 61-64 have been canceled. Claims 1, 27, 52, and 53 have been amended. The application now includes claims 1, 3-27, 29-56, and 58-60.

To accelerate prosecution, the claims have been limited to reversed hexagonal liquid crystalline phase compositions (discussed in the application on page 24, lines 22 et seq.), not normal hexagonal phase liquid crystalline phase compositions (discussed in the application on page 23, line 12 et seq.), and to reversed cubic liquid crystalline phase compositions (discussed in the application on page 26, at line 17, et seq., and at page 28, at line 13 et seq.), not normal cubic liquid crystalline phase compositions (discussed in the application on page 25 at line 11 et seq.). Exemplary formulations are set forth on pages 52 et seq. of the patent application.

As will be demonstrated below, independent claims 1 and 27 are allowable over the prior art of record. In view of this, dependent claims 20-26 and 45-51, which were previously withdrawn, should be rejoined and allowed with the next office action.

Claims 1, 3-19, 27, 29-44, 52, 53, and 56-60 have been rejected as being obvious over a combination of Lambert in view of Benet and Azuma. This rejection is traversed in view of the amendments above, the concurrently filed Declaration of David Anderson under 35 U.S.C. 1.132, and the remarks below.

2. The Office Action.

In the office action on page 2-3, the Examiner made the following statements:

> "Lambert teaches an emulsion comprising surfactants and a therapeutic. Taxol is disclosed as most preferred. Poloxamer 123, selected by applicants, is disclosed. Oral delivery is specified. Antioxidants are disclosed. Benet teaches essential oils to increase the bioavailability of pharmaceutical compounds. Spearmint and taxol are disclosed. Azuma teaches that gentisic acid is an antioxidant.
>
> "It would have been obvious to one of ordinary skill to add an essential oil to the composition of Lambert to achieve the beneficial effect of increasing the bioavailability of taxol in view

> of Benet and to further add gentisic acid to achieve the beneficial effect of an antioxidant in view of Azuma. .... As to the claimed property of a structure fluid, the obvious composition must possess said property because it is the same as that claimed.
>
> "Applicants argue that Lambert does not teach the claimed L3 or liquid crystalline phases. However, it is argued that it is the obvious combination of the same ingredients as claimed in which such phases are formed. Applicant's argument that the addition of spearmint oil per Benet will not produce the claimed phases is mere opinion. Similarly, applicant's argument that, at the levels used in Azuma et al the addition of gentisic acid will not change phase behavior is also mere opinion." (emphasis added)

As best understood, in sum, the Examiner's position appears to be that: (i) it was obvious to add spearmint oil to the Lambert formulation in light of Benet, and it was obvious to add gentisic acid in light of Azuma; and (ii) adding those ingredients together was sufficient to create Applicant's claimed compositions because any two compositions with the same list of ingredients are necessarily the same composition, therefore the Applicant's claimed compositions are obvious.

3. Response

This reasoning of the Office Action is flawed for the following reasons: (i) it is demonstrated by the experimental evidence presented in the Declaration of David M. Anderson (see Table 1 and Figure 1 in Item 3) that the Examiner's conclusion of what composition will be created by the combination of the references is simply wrong; (ii) one of ordinary skill in the art would not mix and match ingredients from references as the Examiner has done; (iii) one of ordinary skill in the art attempting to increase solubilization of actives in a lyotropic liquid crystal system would not have referred to Lambert, Benet or Azuma; (iv) one of ordinary skill in the art attempting to increase solubilization of active in any system whatsoever would not have referred to Lambert, Benet or Azuma; and, (v) one of ordinary skill in the art would recognize that the different morphologies of the different phases of lyotropic liquid crystals are caused by differing concentrations of the same ingredients, and impact characteristics and behavior of the compositions.

a) Experimental evidence and expert testimony establishes that the claimed composition is not created from the combination of references identified by the Examiner.

As is demonstrated by experimental evidence and expert testimony of the inventor in the accompanying Declaration under 37 C.F.R. 1.132, no combination of Lambert, Benet and Azuma would yield a structured fluid that consists of a reversed cubic liquid crystalline phase or a reversed hexagonal liquid crystalline phase (see Item 3 of the Declaration). In order to simplify and accelerate prosecution of the instant application, independent claims 1, 27, 52, and 53 have been limited to compositions where the structured fluid consists of a reversed cubic liquid crystalline phase or a reversed hexagonal liquid crystalline phase. As such, no combination of the references would show or make obvious the claimed invention.

As explained in the patent application, reversed cubic and reversed hexagonal liquid crystalline phases are structured fluids which are lipophillic phases which are not water soluble (as opposed to normal cubic or normal hexagonal phases) and can be readily dispersed in an aqueous medium like water. Dr. Anderson's Declaration, at Table 1 in Item 3, shows that different combinations of the ingredients elected in response to the election of species requirement create radically different compositions, and the combination of Lambert plus Benet's spearmint oil plus Azuma's gentisic acid demonstrably form many different compositions, NONE OF WHICH ARE THE CLAIMED COMPOSITIONS.

The accompanying Declaration makes the experimental evidence of record and the testimony of the inventor, who is an expert in the field of the present invention, of record in the case, and rebuts the conclusions drawn in the last office action and provides more than "mere opinion". (The Examiner should realize, however, experts provide "opinion" evidence that is legally recognizable, and not "mere opinion" that can be ignored). The declaratory evidence and data in the accompanying Declaration of David Anderson has been prepared to assist the Examiner in recognizing that simply mixing of the ingredients of three different references will not result in the claimed subject matter.

b) The premise of the Examiner -- that if one combines the same ingredients one necessarily obtains the same composition -- is not true in the scientific area of lyotropic liquids and liquid crystals where compositions of entirely different morphologies and properties can be created by slight variations in the relative concentration of the same ingredients.

The office action improperly dismisses as "mere opinion" Applicant's previous factual argument, based on well recognized understandings of those of skill in the art (see Declaration of David Anderson at Item 4), that in the scientific field of lyotropic liquids and liquid crystals different combinations of the same ingredients can and do form entirely different materials and morphologies with different properties, and that the mere combination of the ingredients as per Lambert, Benet and Azuma will not create the claimed compositions. However, as is noted in the accompanying Declaration of David Anderson at Item 4, it is a generally recognized and fundamental scientific principle among those in the field that varying the concentration of ingredients in colloidal systems creates radically different compositions. Lyotropic liquid crystals are a class of matter, lipid and/or surfactant based, which self assemble into many different, stable configurations or structures, each with different properties and characteristics. The configurations vary, assuming temperature and pressure are held constant, with the relative concentrations of ingredients to the solvent (hence the term "lyotropic") and thus to one another. See, for example, Figueiredo Neto, Antonio M., and Salinas, Silvio R.A. The physics of lyotropic liquid crystals : phase transitions and structural properties, New York : Oxford University Press (2005) 304 pp (see for example, pp 1, 5 and 112); Zana, Raoul, Ed., Dynamics of surfactant self-assemblies : micelles, microemulsions, vesicles, and lyotropic phases, Boca Raton : Taylor & Francis/CRC Press (2005) 518 pp (see for example pp 348-9); Petrov, Alexander G., The lyotropic state of matter : molecular physics and living matter physics, Amsterdam : Gordon and Breach Science Publishers, (1999) 549 pp (see for example pp 1, 22-3, 26-7 and 40); Evans, D. Fennell and Wennerstrom, Hakan, The Colloidal Domain – Where physics, chemistry, biology and technology meet (2nd Ed.) New York, Wiley-VCH (1999) 632 pp (see for example pp 5, 16-18, 306-308, 494-4 and 501-505) ; Phase Transitions in Liquid Crystals, Martellucci, S. and Chester, A.N., Eds, New York Plenum Press (1992)

505 pp (see for example pp 413, 454-5 and 458-9). (above cited pages reproduced as Attachment A to this Memorandum).

Because of this phenomenon, those skilled in the art of lyotropic liquids and liquid crystals have developed and rely upon the phase diagram (see Figure 1 in Item 3 of the Declaration of David Anderson), a universally recognized device for exploring, capturing and understanding the impact of the variation of the relative concentration of ingredients on the compositions formed from a given set of ingredients. The phase diagram sets forth the different types of compositions created by various concentrations, or ratios, of the same components. Evans and Wennerstrom, The Colloidal Domain – Where physics, chemistry, biology and technology meet, supra at pages 501-505. In Item 5 of his Declaration, Dr. Anderson explains this principle with reference to the three component phase diagram set forth as an illustration in Fennel and Wennerstrom at pp 501-505. That phase diagram was prepared from experimentation using incrementally different variations of the three components, and records what composition was created by each such combination, ranging in that instance from simple colloidal suspensions, to micelles, lamellar phase materials, as well as normal and reversed hexagonal phase materials. Dr. Anderson explains in the Declaration that the compositions which are formed from the combination of the same three ingredients but at various relative concentrations must be determined empirically, are not obvious in advance from the simple list of ingredients, and cannot be predicted a priori based on other three component systems. Thus, it is simply incorrect science to state that two compositions are necessarily identical because they are made of the same ingredients - irrespective of amounts and relative concentrations. Many different compositions are possible, and while there are thermodynamic laws and principles at work which can provide some guidance in certain circumstances and conditions, it is not at all obvious what composition will be produced by any given combination of relative concentrations of the ingredients. Thus, as is evidenced by the Declaration of Dr. Anderson at Item 4 of the Declaration, one of ordinary skill in the art would not expect to combine the teachings of Lambert, Benet and Azuma to achieve the claimed compositions in the instant application; that is, one of ordinary skill in the art simply would have no reason to believe that combination was likely to form reversed cubic or

reversed hexagonal phase material as compared to emulsions or liposomes or other liquid crystalline phases, and hence would not be motivated to make the combination proposed.

As demonstrated in Item 3 of the concurrently filed Declaration, the addition of spearmint oil and gentisic acid to Lambert's mixture creates, depending upon the relative concentrations of the same ingredients, many different compositions with radically different structures, not one and the same composition over and over again. As set forth in Table 1 of the Declaration of Dr. Anderson, 46 different combinations of Lambert's Mixture A with spearmint oil embodying 46 different relative concentrations of the ingredients were prepared, analyzed and recorded in a phase diagram set forth as Figure I. Many different compositions were observed, from liquid to emulsion to normal cubic phase. As is demonstrated by the Declaration of David Anderson at Item 3, the addition of spearmint oil to Lambert's mixture will NOT create reversed cubic or reversed hexagonal liquid crystal phases. This Declaration shows this to be true by demonstrable scientific fact. Reversed cubic or reversed hexagonal phases as claimed by the instant invention are never present when spearmint oil is added to the Lambert mixture. Thus, the result stated in the last office action to be obvious is not only not obvious, but not physically possible.

As demonstrated by the Declaration of David Anderson at Item 3, the further combination of gentisic acid to the Lambert system plus Benet does not form reversed phase cubic or reversed hexagonal liquid crystal phases. Dr. Anderson prepared ten different samples of the Lambert plus Benet combination, added gentisic acid and evaluated the impact on phase behavior. In Item 3 of the Declaration of Dr. Anderson it is noted that in none of these samples did the phase of the material change. Furthermore, as a matter of scientific principle, no amount of gentisic acid could be added to the mixture to create reversed cubic or reversed hexagonal phase material. According to Dr. Anderson's Declaration, at the pH of the Lambert system, gentisic acid will deprotonate and convert to a salt, even if it is not introduced as a salt. As stated in the present application in the section entitled "Synergistic effects", when a phosphatidylcholine-water mixture is converted to a non-lamellar phase by the addition of an essential oil or other compound, then the addition of gentisic acid salts such as gentisic acid

ethanolamine, and related compounds, have a tendency to cause the mixture to revert back to lamellar. Phrased otherwise, gentisic acid salts push the phase behavior of surfactant systems away from reversed, toward lamellar (and ultimately toward normal phases). Consequently the addition of gentisic acid to Lambert would teach away from that which is described and claimed in the instant application. This follows from the high hydrophilicity of gentisic acid salts, which have an octanol-water partition coefficient at pH 8 of logD=-2.5 (negative 2.5), as calculated from Advanced Chemistry Development's software package, meaning that gentisate partitions very strongly into water over oil. Highly water-soluble, low Kow compounds (as implied by a high HLB) do not induce reversed liquid crystalline phases, rather they promote normal Type I phases. Dr. Anderson added gentisic acid in an amount greater than would be used in a typical antioxidant in a pharmaceutical formulation, and still did not observe any change in phase or the appearance of any reversed cubic or reversed hexagonal phase material. The addition of lesser amounts of gentisic acid would have even less impact.

c. The problem faced by the inventor in the present application was how to solubilize a difficult to solubilize active for incorporation into a reversed phase lyotropic liquid crystalline material, and to one of ordinary skill in the art none of the cited references bears any relationship to or provides any guidance for addressing that problem.

The claimed invention is focused on a particular problem involving reversed cubic and hexagonal phase materials. The problem is how to incorporate specific drugs which are particularly difficult to solubilize into this particular delivery vehicle. The inventor explored an approach of co-solubilizing the drugs with an additional component as a means of increasing solubility of insoluble drug sufficient to incorporate into and create a lyotropic liquid crystal, specifically a reversed cubic or reversed hexagonal phase. The inventor discovered that it helps to get hydrophobic agents somewhat solubilized in a component oil phase so that it can become an integral part of the long range order of the membrane. The application describes and claims the discovery that a variety of compounds (such as essential oils, and vitamin E) can solubilize a variety of actives to get them into an oil phase, allowing the incorporation of the compound in a reversed cubic or

reversed hexagonal phase lyotropic liquid crystal: (i) when that would not have been possible without the use of those compounds in that manner; and (ii) without shifting the morphology away from the reversed cubic or reversed hexagonal phases by the addition of those compounds into the system. The invention is new and unobvious, and is not limited to the specific compounds set forth in the application. However, it should be recognized that the application claims a composition made of certain ingredients that surprisingly form a certain structure – a reversed cubic or reversed hexagonal liquid crystalline phase. Both the components and the structure are elements of the Claims.

Lyotropic liquids and liquid crystals are extraordinary materials, and their study is specialized. This is an area of science which does not arise in Lambert, Benet or Azuma, and for which those patents provide no teaching whatsoever. The specific issue of incorporating a compound which does not readily incorporate into a lyotropic liquid crystal is not involved in Lambert, Benet or Azuma. None of the three references even mentions phase behavior, thus, one of ordinary skill in the art would not look to the three references to provide guidance on preparing reversed cubic or reversed hexagonal liquid crystalline phases. Lambert explicitly deals with emulsions only. Benet and Azuma are not concerned with the morphologies or phases of compositions. There is neither mention nor recognition that liquid crystalline phase structured compositions are radically different from other structures. Emulsions, for example, are combinations of large amorphous homogenous oily regions within an aqueous medium (or vice versa), separated by surfactant. No lipid bilayer is present. Reversed cubic phase materials are bicontinuous aqueous channels created by and interlaced with a continuous lipid bilayer with long range order on the nanometer scale. Clearly the specific problem faced by the inventor, solubilizing a hard to solubilize drug with a co-solubilizer in such a way as to promote formation of a reversed cubic or reversed hexagonal phase structure, is not involved at all in Lambert, Benet or Azuma. Nor is solubilization generally. Indeed, Lambert's use of emulsions is a completely distinct approach to delivering taxol, in which there is no effort made to solubilize the drug but rather just the opposite. Lambert uses the emulsion to sequester the drug in the emulsion's oily domains, which are maintained separate from the aqueous milieu by stabilizers. Any increase in

solubility of taxol in Lambert would have ruined his composition, as it would have broken down the stark divisions between oily domains and water domains which are the essence of emulsions. While Benet teaches the use of essential oils such as spearmint for increasing bioavailability, Benet has nothing to do with solubilizing a drug, let alone incorporating the essential oil or drug into a lyotropic liquid crystal. According to Benet, essential oils increase the bioavailability of a drug by interfering at the cellular level with intricate molecular reflux systems, pGp and Cyp3A, which are built into and around the cell membranes and which screen and pump out of the intracellular space molecules which are foreign to the cell. There is no mention whatsoever about solubilization, and certainly nothing whatsoever related to the morphology of the drug delivery vehicle.

The Azuma reference is even more irrelevant. The Examiner's argument is that "antioxidants are disclosed" in Lambert, Azuma identifies gentisic acid on a long list of antioxidants, and therefore it would be obvious to combine Lambert with Azuma. As noted above, and in the Declaration of David Anderson one skilled in the art would have no reason to believe that gentisic acid combined with the other references at levels typically used for antioxidants in pharmaceutical formulations would impact solubility of the active or promote the formation of reversed cubic or reversed hexagonal phase materials. Furthermore, the evidence presented in Dr. Anderson's Declaration demonstrates that the combination does not in fact yield reversed cubic or reversed hexagonal liquid crystalline phases. Azuma has nothing to do with solubility of an active or with lyotropic liquid phases or the delivery of active pharmaceutical agents. The closest link in the Examiner's argument is Lambert. What Lambert actually says is:

> "The emulsions of the invention can comprise an aqueous medium. The aqueous phase has an osmolality of approximately 300 mOsm and may include potassium or sodium chloride sorbitol, mannitol, polyethylene glycol, propylene glycol albumin, polypep and mixtures thereof. This medium can also contain various additives to assist in stabilizing the emulsion or in rendering the formulation biocompatible. Acceptable additives include acidifying agents, alkalizing agents, antimicrobial preservatives, antioxidants, buffering agents, chelating agents, suspending and/or viscosity-increasing agents, and tonicity agents." (emphasis added)

As will be recognized, the groups of additives listed in Lambert include eight other broad categories of compounds as well as antioxidants, and the compounds in those groups collectively number in the hundreds, if not thousands. Lambert gives no guidance for choosing antioxidants over any of the other groups of compounds listed, and certainly not for choosing gentisic acid over other antioxidants: except, however, that they are recommended for the purpose of assisting in stabilizing the emulsion or in rendering the formulation biocompatible. Neither purpose was an issue in the instant invention: the inventor was not working with emulsions but instead an alternative and fundamentally different technology to emulsions, and biocompatibility is not an issue. Most importantly though, neither Lambert nor Azuma show or suggest anything related to obtaining reversed cubic or reversed hexagonal liquid crystalline phase materials (this is not surprising because the concurrently filed Declaration of David Anderson shows this is a physical impossibility). Rather than providing any guidance on increasing solubility of a compound into a lyotropic liquid or liquid crystal, Lambert is completely focused on emulsions. Thus, the addition of an ingredient that produced something other than an emulsion would essentially teach away from that which is desired by Lambert. Furthermore, nothing in Lambert suggests he was looking to increase oral bioavailability or reduce oxidation. Therefore, it would not be obvious to one of ordinary skill in the art to use the teachings of Benet or Azuma. Moreover, Benet and Azuma are not concerned with solubilizing a pharmaceutical agent (instead, that is taken as a given in Benet and Azuma).

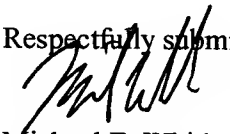
4. Conclusion

Given the amendments above, the data and expert opinion provided in concurrently filed Declaration of David Anderson which demonstrates that the claimed reversed cubic phase and reversed hexagonal phase liquid crystalline phases cannot be made by using ingredients from the Lambert, Benet and Azuma references, as well as the explanations and arguments presented above, claims 1, 3-27, 29-56, and 58-60 should now be in immediate condition for allowance. Reconsideration at an early date is requested.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at the local telephone number listed below to discuss any other changes deemed necessary in a telephonic or personal interview.

A provisional petition is hereby made for any extension of time necessary for the continued pendency during the life of this application. Please charge any fees for such provisional petition and any deficiencies in fees and credit any overpayment of fees to Attorney's Deposit Account No. 50-2041.

Respectfully submitted,



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